TOPICAL REVIEW

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To cite this article: Panneerselvam Theivendren *et al* 2025 *Nanotechnology* **36** 122003

IOP Publishing Nanotechnology

Nanotechnology **36** (2025) 122003 (20pp) https://doi.org/10.1088/1361-6528/adad7a

Topical Review

Surface receptor-targeted protein-based nanocarriers for drug delivery: advances in cancer therapy

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Received 3 November 2024, revised 30 December 2024
Accepted for publication 23 January 2025
Published 30 January 2025

Abstract

Significant progress has been made in cancer therapy with protein-based nanocarriers targeted directly to surface receptors for drug delivery. The nanocarriers are a potentially effective solution for the potential drawbacks of traditional chemotherapy, such as lack of specificity, side effects, and development resistance. Peptides as nanocarriers have been designed based on their biocompatible, biodegradable, and versatile functions to deliver therapeutic agents into cancer cells, reduce systemic toxicity, and maximize therapy efficacy through utilizing targeted ligands such as antibodies, amino acids, vitamins, and other small molecules onto protein-based nanocarriers and thus ensuring that drugs selectively accumulate in the cancer cells instead of healthy organs/drug release at a target site without effects on normal cells, which inherently caused less systemic toxicity/off-target effect. Moreover, their intrinsic protein backbone naturally degrades *in vivo*, providing another level of safety over synthetic materials. Various issues like immunogenicity, mass production, and quality control must be addressed for widespread use. However, further studies are necessary to perfect protein engineering and improve drug loading, protein modification, and targeting. Thus, it can be concluded that protein-based nanocarriers targeted against the surface receptors would help achieve cancer management in a more focused manner, thus minimizing toxicity. The further development of these nanoparticles could bring a significant change in cancer treatment so that more personalized, targeted, and safe therapies would be available to all patients.

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Keywords: protein-based nanocarriers, cancer therapy, surface receptor-targeting, drug delivery, biocompatibility, cancer specificity

1. Introduction

A group of complex and multifaceted diseases known as 'cancer' are characterized by uncontrollably growing and dividing cells that can spread to other parts of the body [1]. Cancer is caused by mutations that change how cells respond to growth signals, problems with the cell death mechanism, and an enhanced capacity to penetrate tissues and produce new blood vessels [2]. There are almost 200 different types of cancer, named after the organ or tissue where they can originate, and each one has a unique diagnosis and course of treatment [3]. Cancer-related mortality rates rank second globally behind deaths from disorders of the cardiovascular system and are regarded as the most important global health concern [4]. The International Agency for Research on Cancer, the World Health Organization's (WHO) cancer agency, published the most recent estimates of the worldwide cancer burden ahead of World Cancer Day as part of universal health coverage; WHO also released survey data from 115 countries, demonstrating that the majority of them do not sufficiently fund key cancer and palliative care treatments. An estimated 9.7 million people died from cancer, and 20 million new cases were reported in 2022. It was projected that 53.5 million people survived five years after receiving a cancer diagnosis. One in five persons will have cancer in their lifetime, and one in nine men and one in twelve women will pass away from it [5]. Disparities in cancer burden and mortality exist between high and low high-development index (HDI) countries. Cancer cases are projected to increase to 35 million by 2050, particularly in low and medium-HDI countries, highlighting the need for improved healthcare infrastructure and access to cost-effective cancer medicines [6].

Currently, several treatment strategies are followed for cancer, including chemotherapy, surgery, radiation and laser therapies, immunotherapy, hormone therapy, monoclonal antibody therapy, combination therapy, etc [7]. Chemotherapy is ideal for the clinical treatment of various types of cancers [8]. Chemotherapies are harmful because they attack not only malignant cells but also healthy cells that are fast multiplying, like the intestinal epithelium and bone marrow cells. This can lead to severe side effects and treatment failure [9]. Also, some chemotherapies have hydrophobic or hydrophilic characteristics; these are failures to reach the cancer site. However, these drugs show significant cytotoxicity against cancer cells in *in vitro* studies [10]. Therefore, improving chemotherapy's bioavailability, selectivity, and therapeutic index to cancer cells and decreasing toxicity to healthy cells is a central issue in effective cancer treatment.

On top of that, chemotherapy only works for so long. Cancers eventually become resistant to the regimen, and treatment is less effective. Figure 1 shows the challenges of conventional therapy and highlights the necessity of devising treatments for cancer that are less toxic and more selective. Traditional cancer treatments, and especially chemotherapy, cause much toxicity. Because chemotherapeutic agents are not selective and can affect any rapidly dividing cells in the body (e.g. those of hair, bone marrow cells, gastrointestinal tract), they tend to cause side effects such as alopecia and suppression of normal cell production (red/white blood cells). These non-specific effects have a wide range of adverse impacts, e.g. immunosuppression, nausea, vomiting, and hair loss. This high toxicity also means the amount of chemotherapy that can be administered is restricted, so it may not work as well [11, 12].

Drug resistance is yet another significant drawback in the treatment of cancer. However, cancer cells can also develop resistance mechanisms to evade the effects of chemotherapy, such as by changing drug targets, increasing drug efflux, and so on. Consequently, patients respond to the treatment at first but ultimately relapse with an important drug-resistant persistent disease. Traditional cancer therapies are not targeted, resulting in damage to healthy as well as malignant cells. Such a lack of specificity not only adds to toxicity but also ultimately hampers treatment response. One of the main objectives in modern cancer therapy is how we can kill, specifically tumour cells and less normal tissues, to enhance treatment results with minimal side effects [13].

In this scenario, a novel surface receptor-targeted drug delivery system (DDS) was developed to recognize and bind the up-regulated receptor molecules on cancer cells and to deliver the chemotherapeutic agent without disturbing the healthy cells or tissues. Scientists have found a way to modify these carriers to only recognize and bind surface receptors on cancer cells, essentially targeting the DDS specifically at lymphoma [14, 15]. Therefore, this review will summarize current reports and recent advances in surface receptor-targeted protein-based nanocarriers as a new proficient cancer treatment method. Surface receptor-targeted DDSs (TDDSs) are being tested for their ability to target cancer cells more directly, which could increase treatment efficacy and decrease toxicity. It may even be possible to eliminate the negative effects of immune system damage and the loss of rapidly replicating cells.

2. DDSs

Due to the low therapeutic efficacy of these pharmaceuticals, various DDSs have been developed with the purpose of improving the pharmacological properties of drugs by increasing their bioavailability, stability and targeting efficiency. For the past few decades, considerable research has

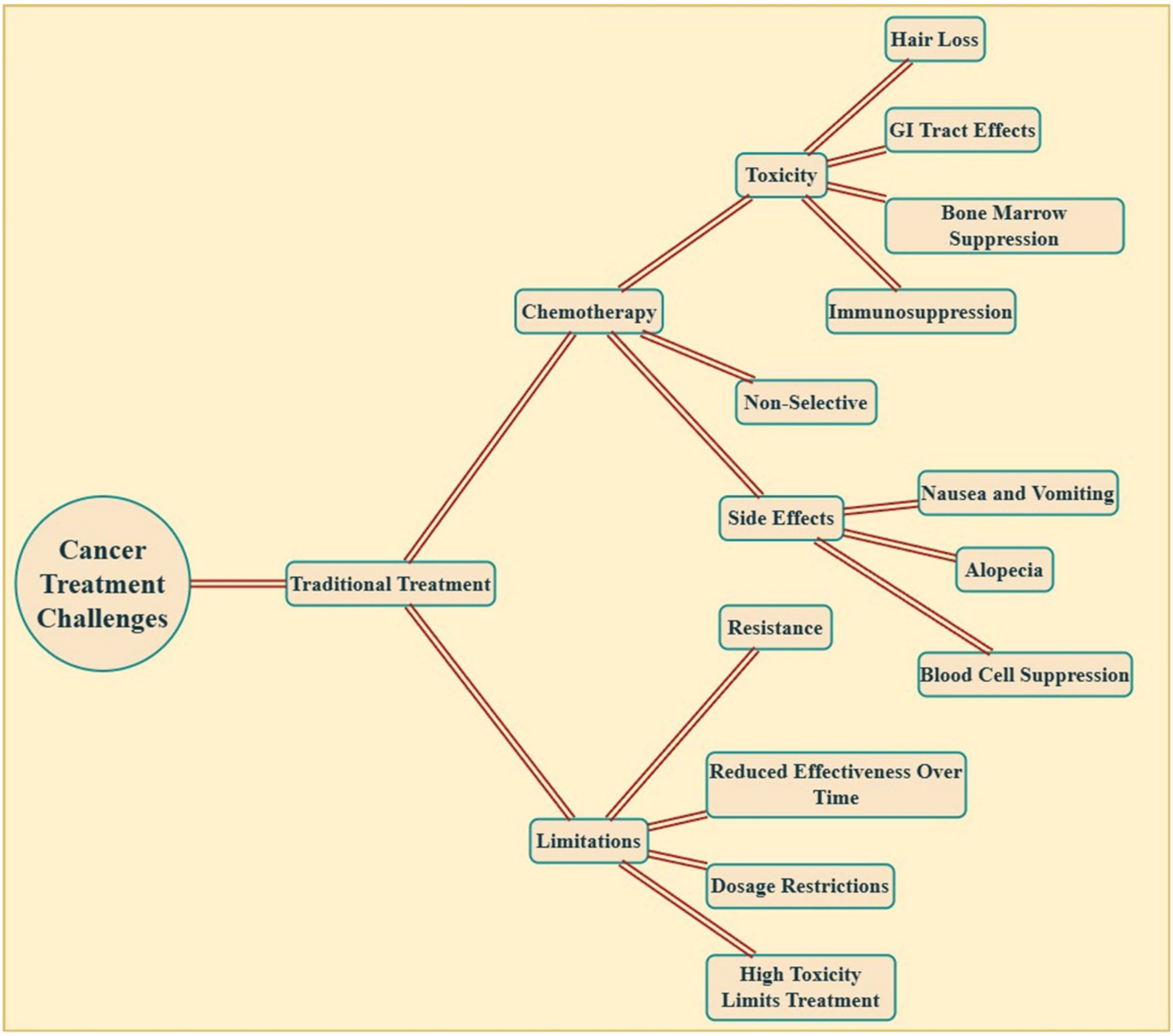

Figure 1. Diagram illustrates the challenges associated with traditional cancer treatments, emphasizing chemotherapy's non-selective toxicity, side effects, resistance, and dosage limitations that impact treatment efficacy and patient well-being.

been performed to design conventional and TDDSs that can overcome the limitations associated with traditional cancer therapies figure 2.

Traditional drug delivery, by methods such as oral or intravenous administration, uses passive distribution of drugs in the body. Consequently, many drugs behave sub-optimally at tumoral levels before hitting normal tissues with a more consistent circulation and are eliminated from the body. A consequence of this is that cancer-specific therapeutic concentrations are not likely to be reached unless doses are in the range associated with toxicity or adverse effects.

The purpose of TDDS is to maximize the effectiveness and reduce any side effects so that drugs are directed autonomously toward a desired organ. Such systems frequently use unique properties of cancer cells, in this case, the fact that certain surface receptors are over-expressed, to allow drug or nanoparticle recognition. TDDSs can deliver drugs directly to cancer cells, allowing them to reach a required dose and reducing off-target effects otherwise associated with treatment. However, an encouraging approach in TDDS is the application of carriers at the nanoscale that can be modified to facilitate carrying drugs and target receptors on cancer cells [16, 17].

3. Mechanisms for targeting exerted by surface receptors

Targeting of surface receptors become a promising method for drug delivery in cancer treatment to enhance the specificity and therapeutic activity with minimal side effects. One important aspect of cancer eradication is protein binding (receptors) on the membrane surface of cancer cells that work in various biological reactions such as cell growth, differentiation and survival. Protein-based nanocarriers targeted to these receptors accomplish the specific delivery of cytotoxic drugs at tumour sites, improving therapeutic efficacy [18, 19].

3.1. The role of surface receptors in cancer cells

Surface receptors play an important role in cellular function regulation, such as signal transduction, cell adhesion

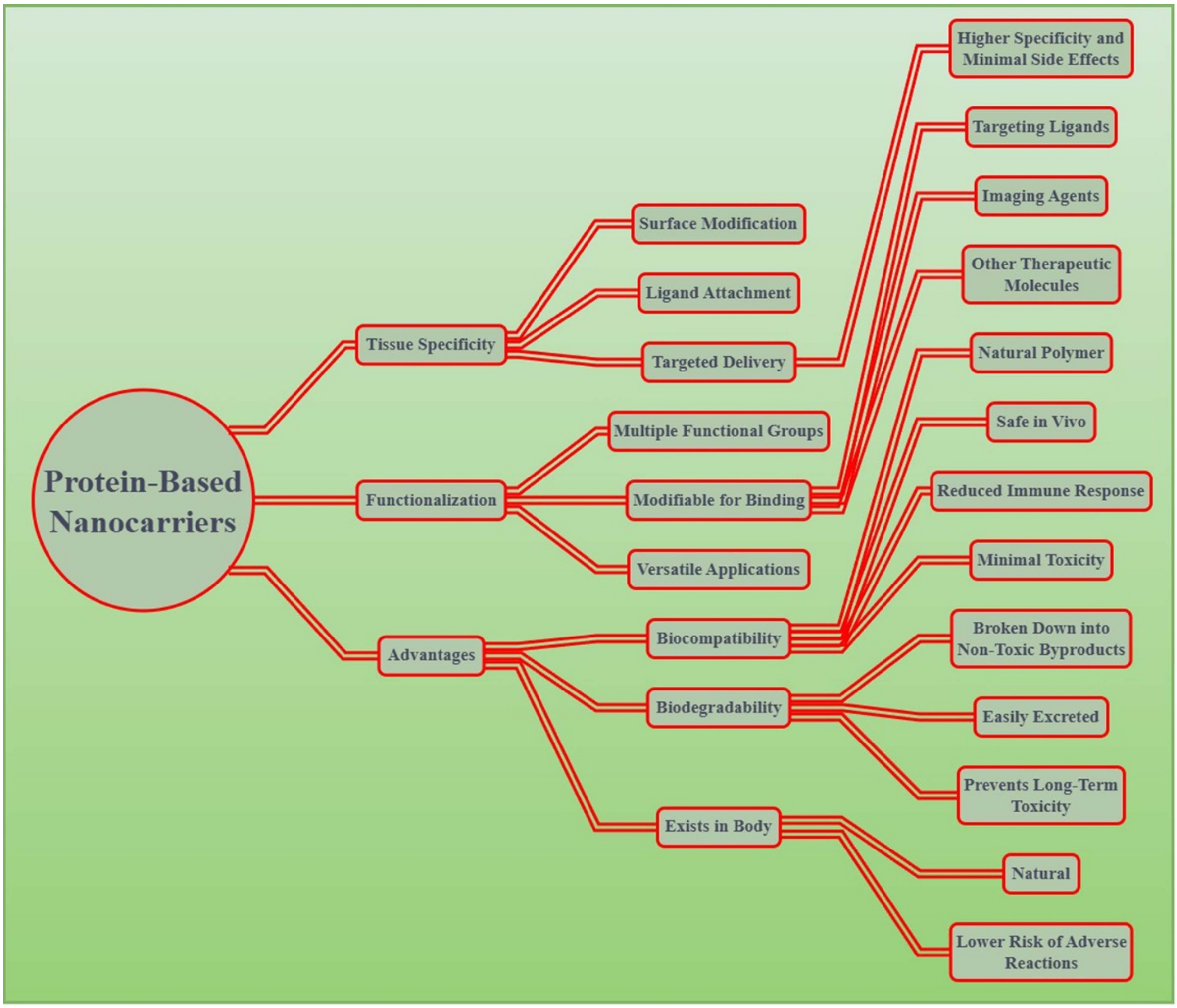

Figure 2. Diagram highlights the advantages of protein-based nanocarriers, showcasing their tissue specificity, biocompatibility, biodegradability, functionalization capabilities, and versatile applications in targeted drug delivery and cancer therapy.

and immune response. But, in many cancers, these receptors are overexpressed, mutated or dysregulated and play a role in uncontrolled cell proliferation and metastasis resistance against therapy. If nanocarrier-based therapeutics could be specifically directed at these overexpressed receptors, it would make drug delivery tenfold easier on the cancer cells and also help reduce systemic toxicity [20, 21].

3.2. Receptor rearrangements and the onset of cancer

Several surface receptors are often associated with specific types of cancer; for instance, human epidermal growth factor receptor 2 (HER-2), epidermal growth factor receptor (EGFR) and the folate receptor. HER-2 and EGFR expression are well known in aggressive brain cancer (via HER-2 over-expression) or for lung/colorectal cancers where EGFR dysregulation is a frequent oncogenic event. In ovarian cancer, folate receptors are abundantly expressed. These rearrangements of the function of the receptor turn on cell signaling pathways in a dysregulated manner, leading to cancer initiation and progression, thereby promoting tumorigenesis figure 3. The nanocarriers may be combined with therapies targeted at these receptors to break down the pathways and prevent cancer growth [22, 23].

3.3. Ligand-receptor interactions

The ligand-receptor interactions are the basis for receptor-targeted drug delivery. These ligands, such as antibodies, aptamers and peptides, can be home to the receptors of cancer cells with high specificity, causing cellular uptake target nanocarriers drug encapsulated contents. It also improves the drug to accumulate in cancer cells leading to more potent and targeted therapy [24, 25].

3.4. Active versus. Passive targeting

For active targeting, drug-loaded nanocarriers can be decorated with ligands that bind specifically to overexpressed surface receptors on cancer cells, promoting receptor-mediated endocytosis and internal uptake of the carrier. On the other hand, passive targeting utilizes enhanced permeability and retention (EPR) impacts so that nanocarriers can collect in

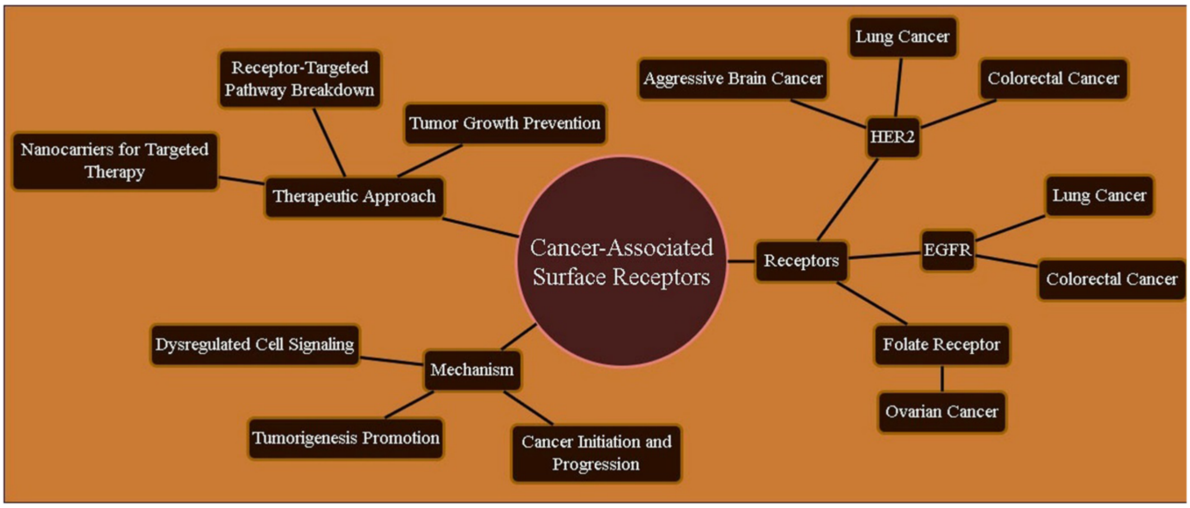

Figure 3. Diagram highlights cancer-associated surface receptors, their roles in tumorigenesis, and therapeutic approaches using nanocarriers. It details receptors like HER2 and EGFR, targeting various cancers, including lung and colorectal.

cancer tissues because of their leaky vasculature. Passive targeting, on the other hand, is relatively non-specific and, thus, active targeting enables a site-directed drug delivery that indiscriminately affects only cancer cells [26, 27].

3.5. Ligands for receptors

Numerous ligands can be employed to prepare protein nanocarriers for receptor targeting, all of them having some advantages with regard to specificity and binding affinity [28, 29]. Table 1 lists various ligands conjugated protein nanocarriers for targeting cancers.

3.5.1. Antibodies. Monoclonal antibodies (mAbs) are the most specific ligands that can be used to provide targeted drug delivery because of their high specificity for a target receptor, such as HER2 or EGFR, with strong binding affinity [40, 41].

3.5.2. Aptamers. Aptamers are small molecules of single-stranded nucleic acids forming a unique three-dimensional structure, allowing them to bind specifically cognate receptors. High specificity and low immunogenicity [42, 43].

3.5.3. Peptides. Whereas peptides are short amino-acid chains that behave similarly to the natural ligands of surface receptors and, as such, provide flexible structures with low production costs in terms of synthesis [44, 45].

3.6. Target-receptors for protein-based nanocarriers

Functionalization of protein-based nanocarriers like albumin, transferrin and antibodies for cancer cell surface receptors specific targeting. Due to their great stability in the structure, biocompatibility and extreme adaptability to what is desired of controlled release, nanocarriers have been very useful as carriers for therapeutic agents, especially against tumor [46, 47].

3.7. HER-2 targeting in breast cancer

HER-2 overexpression is restricted to 20%–30% of breast cancers. Selective drug delivery to HER2+ tumors using nanocarriers conjugated with antibodies such as trastuzumab (Herceptin) enhances treatment efficacy and improves patient prognosis [48, 49].

3.8. EGFR targeting in lung and colorectal cancer

It is a common site of overexpression and mutation, which has led to it being studied closely in varieties of tumor types best exemplified through lung (non-small cell) cancer and colorectal malignancies. Nanocarriers aiming at EGFR can efficiently deliver chemotherapy or small-molecule inhibitors directly to the tumor, thereby blocking resistance mechanisms and potentiating drug efficacy [50, 51].

3.9. Folate receptor-targeting in ovarian cancer

Folate receptor is frequently overexpressed in ovarian cancer. Functionalizing nanocarriers with folate or its derivatives has enabled selective drug delivery at the cancer cells level, minimizing non-specific cytotoxicity and maximizing therapeutic efficacy. Protein-based nanocarriers with surface receptor targeting are the next line of attack for cancer therapy, yielding a targeted approach in drug delivery to malignant cells that are without toxicities, leading to patient-specific improved outcomes against varied types of cancers [52, 53].

4. Protein-based nanocarriers

Protein-based, which is hydrophilic and less toxic compared to synthetic polymers commonly used as drug delivery carrier materials with biocompatibility features (i.e. being degraded into amino acids), the potential of ligand-to-ligand glamorization due to distinct side chain residues for selective targeting

Table 1. Various ligands conjugated protein nanoparticles for targeting different cancer cells.

Protein	Ligand conjugation	Targeting surface receptor	Loaded drug	Cancer types	References
Bovine serum albumin	Folic acid	Folate receptor	Myricetin	MCF-7 cells (breast cancer cells)	[30]
Human serum albumin	Monoclonal antibody	$\alpha v\beta 3$ integrin	Doxorubicin	M21 cells (Melanoma cells)	[31]
Glutenin	Folic acid	Folate receptor	Retinoic acid	MCF-7 cells (breast cancer cells)	[32]
Soy protein	Folic acid	Folate receptor	Doxorubicin	MCF-7 cells (breast cancer cells)	[33]
Bovine serum albumin	Folic acid	Folate receptor	Chrysin	MCF-7 cells (breast cancer cells)	[34]
Human serum albumin	TRAIL/transferrin	Death receptors (DR4 and DR5)	Doxorubicin	MCF-7 cells and HCT 116-xenografted nu/nu mouse	[35]
Protein-lipid hybrid nanoparticles	Transferrin	Transferrin receptor	Cisplatin and Docetaxel	H1975 cells (lung cancer cells)	[36]
Human serum albumin	Biotin	Biotin receptor	Methotrexate	4T1 cell line (Breast tumor)	[37]
Albumin	Folic acid	Folate receptor	Cabazitaxel	HeLa cells (Cervical Cancer)	[38]
Zein	Folic acid	Folate receptor	Paclitaxel	KB cells (Epidermal carcinoma)	[39]

remains a popular choice in research on various types of nano-carriers. Proteins are natural biopolymers with unique characteristics allowing developers to design uniquely suited drug delivery nano-carriers [54].

Protein-based nanocarriers have gained a lot of interest in the past few years because they offer several important advantages, such as (i). Biocompatibility: Since protein is a natural (or biologically derived) polymer which our body can easily metabolize, applying this carrier system *in vivo* should be highly safe from potential adverse effects. This is a substantial improvement over synthetic materials in that it mitigates the chances of an immune response or toxicity. (ii). Biodegradable: Proteins are biodegradable; for a fact, they can be broken down into non-toxic by-products which are readily excreted from the body. This could be particularly serious when leading to non-biodegradable materials of nanoparticulate delivery systems, which can accumulate in tissues and result in long-term toxicity. (iii). Natural: Proteins are natural, and many already exist in the body. This natural starting point makes protein-based nanocarriers less likely than other types to set off a chain reaction of nasty processes against them. (iv). Tissue Specificity: Protein-based nanocarriers, by modifying surface characters or attaching various ligands, can be used to target specific tissues, rendering higher specificity. This makes it easy to deliver drugs right where needed for treatment with minimal side effects off-target. (v). Functionalization: Proteins have many functional groups that can be modified to bind targeting ligands, imaging agents or other molecules. This versatility allows protein-based nanocarriers to be easily tailored for various therapeutic applications [55, 56].

The aim of this review article is to provide an overview of the most recent advances in using protein-based nanocarrier systems for cancer therapy, with a special focus on the surface receptor targeted approach. In particular, cancerous cells have the ability to proliferate under out-of-control circumstances by expressing surface receptors of various types (responsible for signaling and/or nutrient capture) in excess. In this context, these receptors are the target molecules, those protein-based nanocarriers that can maximize the drug concentration in cancer cells (overcome toxicity) and improve therapeutic effects when using corresponding targeting molecules. Surface receptor-targeted strategies: In this review, we will consider several methods for targeting surface receptors on cancer cells through ligand-receptor interactions and/or antibodies or peptides for receptor targeting.

Recent developments in protein-based nanocarriers: We will discuss recent progress for the designing and engineering of protein-based nanocarriers, such as advancements on direct modification/functionalization of proteins or loading strategies. We will discuss current clinical applications of protein-based nanocarriers, ongoing clinical trials with these nanostructures, and future directions for exploration in this avenue figure 4. Protein-based nanocarriers have been raised as a new strategy in the targeted cancer therapy landscape, indicating that such carriers could be suitable for better and tailored treatment outcomes with less toxicity due to improved characteristics of targeting delivery. Therefore, nanocarriers that employ surface receptor-targeted strategies may be the future to advance more potent and personalized cancer therapy [57, 58].

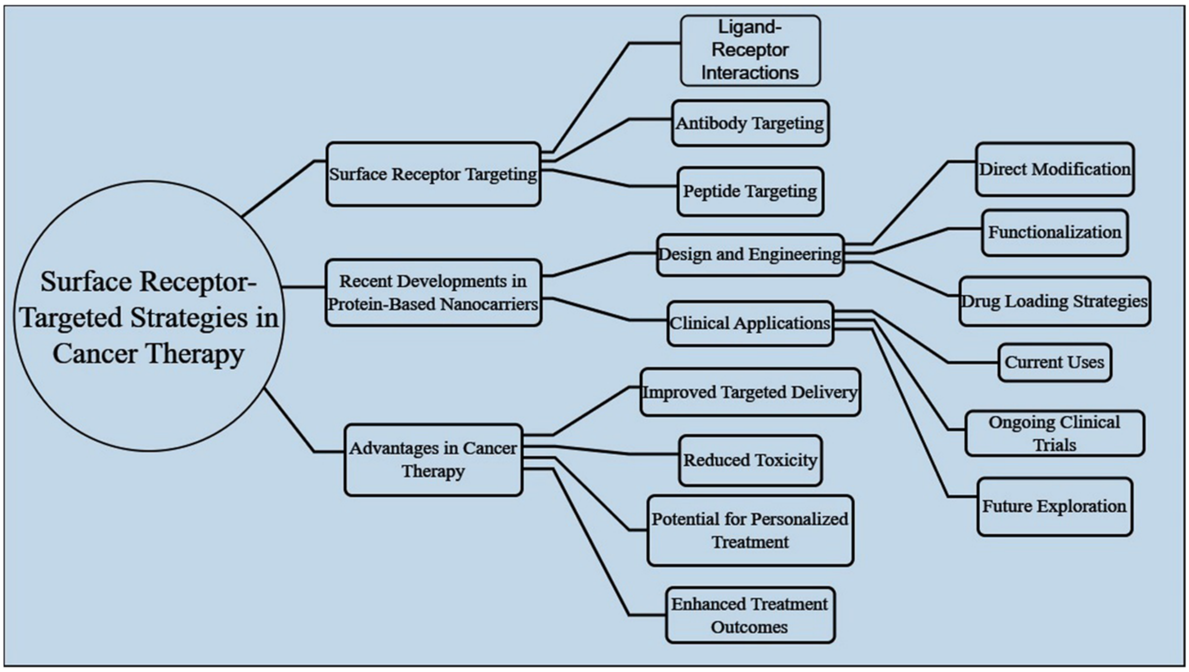

Figure 4. Diagram outlines surface receptor-targeted strategies in cancer therapy, focusing on protein-based nanocarriers. It highlights receptor targeting, design advancements, clinical applications, and therapeutic advantages, including reduced toxicity and personalized treatment.

5. Cancer cell surface receptors

Each type of cancer cell has a distinct arrangement of upregulated surface molecules that serve as potential targets for drug design and imaging to treat cancer [59] effectively. Upregulated cell surface molecules have been identified on cancer cells whose expression appears to be related to malignant transformation, tumor progression, or patient prognosis [60]. Among these cell surface molecules, various cell adhesion molecules, hormones, growth factor receptors, cytokines, proteinases, and their receptors and inhibitors have been identified as potentially useful prognostic markers [18]. This receptor type spans the plasma membrane and performs signal transduction, converting an extracellular signal into an intracellular signal [61]. Their upregulation indicates modifications in the epigenetic code that govern their migration, survival, and escape strategies [62]. These upregulated surface molecules (receptors) help to understand cancer biology and valid drug targets for cancer intervention [63]. Delivering toxic payloads intending to eliminate cancer cells with high concentrations of particular receptors is one tactic. Drug delivery for effective cancer treatment can be achieved by attaching a hazardous payload to a ligand or antibody that recognizes and binds to a receptor.

6. Surface-receptor-TDDSs

DDSs targeting upregulated surface receptors can effectively treat cancer by increasing the bioavailability of drugs at the target site, improving selectivity without interfering with healthy cells, minimizing side effects, and decreasing the likelihood that cancer cells will resist the drugs [64]. Targeting cancer cells with drugs that are specific to the drugs functionalized with cancer recognition moiety (ligand) through appropriate linkers (conjugation chemistry) that recognize and bind themselves to the desired surface receptor, which is either exceptionally expressed or upregulated on the target cells compared to normal tissues/cells, is the basic idea behind surface-receptor TDDSs [65]. The main focus of a surface-receptor-targeted strategy for drug delivery to malignant cells will be on tactics that raise the therapeutic index while avoiding toxic side effects [66]. This refers to the targeted delivery of drugs to cancer cells while sparing healthy cells; additionally, the conjugate must be compatible with blood circulation and quickly broken to release a fresh active cytotoxic agent [67]. Importantly, surface-receptor targeted drug delivery strategies can be achieved by specialized drug carriers (cargo) such as metals, proteins, peptides, nucleotides, lipids, liposomes, polysaccharides, carbon nanotubes, and biodegradable synthetic polymers [68]. Among the various carrier materials, protein and peptide carriers are more suitable for the development of surface-receptor TDDSs because they are natural, easy to alter their surface and conjugate targeting ligand, biocompatible and biodegradable, and cost-effective [69].

Surface-receptor-targeted drug delivery is a cutting-edge tactic that minimizes the relative drug concentration at undesirable sites by selectively delivering drugs to sites of interest [70]. This method has several benefits over traditional dosing forms. A successful receptor-TDDS has four features: retaining, evading, targeting, and releasing [71]. It is important to load drugs properly into a vehicle that can avoid being detected by the body's secretions [72]. To enable efficient drug functioning, the system should have a prolonged residence in

Table 2. The common receptor overexpression profile associated with different types of cancer [18].

Cancer cells	Overexpressed surface receptor	Targeting ligands
Breast cancer cells	Folate receptor	Folic acid
	Glucose	Glucose, glucosamine
	Mannose	Mannose
	Chemokine	Protein, peptide
	Transferrin	Antibody
	Integrin	Cyclic RGD peptide
Lung cancer	Folate	Folic acid
	Integrin	Cyclic RGD peptide
	Amino acid	Amino acid
	Sialic acid receptor	Sialic acid
Liver cancer	Asialoglycoprotein	Lactobionic acid, galactose, N-acetylaminogalactosyl (GalNAc) residues
	Sialic acid receptor	Sialic acid
	Glypican-3	Anti-GPC3 monoclonal antibodies
	Glycyrrhetinic acid receptor	Glycyrrhetinic acid
Brain cancer	Integrin	Cyclic RGD peptide
	Transferrin	Antibody
	Mannose	Mannose
Ovarian cancer	Folate	Folic acid
	Chemokine	Protein, peptide
Colon cancer	Integrin	
	Folate	Folic acid
Prostate cancer	Prostate-specific membrane antigen	PSA antibody

the body and deliver the drugs at the site of action within a reasonable amount of time [73]. Targets and drug carriers are the two main design factors used in DDSs. Drug carriers are how attached medications are delivered to the target site; the target is any diseased organ, tissue, or cell that has to be treated [74]. Recently, many surface receptors have been explored for TDDSs as being overexpressed on various types of cancers, for instance, folate receptor, asialoglycoprotein, mannose receptor, prostate-specific membrane antigen, carbonic anhydrase IX (CA 9), biotin, αv-integrin, transferrin, EGFR, estrogen, androgen receptors, and so forth. The review discusses the recent developments in surface receptor-targeted protein-based nanocarrier delivery systems and commonly used ligands for targeting chemotherapies [18]. Table 2 summarizes the cancer cell-surface receptors and their targeting ligands.

7. Protein-based nanocarriers in drug delivery

Protein-based nanocarriers are the most suitable platforms for targeted drug delivery and have potential applications in cancer therapy owing to their distinct properties [75, 76]. They are exciting because they are relatively safe and easy to prepare, and their size distribution can be easily monitored. They are also amendable to various modifications to incorporate functional and targeting capabilities. Such carriers use proteins' biocompatibility and versatile structural nature to deliver therapeutic agents efficiently. In addition, delivery via protein-based nanocarriers has been reported to overcome multidrug resistance (MDR) caused by drug efflux transporters such as the P-glycoprotein (P-gp), frequently overexpressed in cancer cells. Various protein-based nanocarriers (e.g. albumin, zein, polypeptide, glutenin, protein-synthetic polymer conjugate) have demonstrated efficacy both *in vitro* and *in vivo*. To achieve higher specificity, protein-based nanocarriers can be surface-modified with ligands that specifically recognize receptors on tumour cells. Combining passive and active targeting in a single platform may further improve the therapeutic index of nanocarrier-delivered drugs. The potential to direct against overexpressed surface receptors in cancer cells has enabled nanocarriers made of proteins to be more effective and less toxic for practical applications regarding anticancer drugs. Table 3 demonstrates the various protein-based nanocarriers for targeting surface-receptor-mediated DDSs. The various protein-based nanocarriers, their classification and the beneficial effects of these carriers during cancer therapy are explained in this section [76].

7.1. Majorly used protein-based nanocarriers

Majorly used protein-based nanocarriers for cancer drug delivery applications and their structural composition and functional-perspective [12]. Lipoproteins are endogenous protein-lipid assemblies of the human body, representing an essential lipid transporter. Synthetic or reconstituted lipoproteins may be manipulatively composed to package hydrophobic drugs that act as a carrier for drug delivery, which can be transported in the body like their physiological counterpart. Nature-inspired lipoprotein nanocarriers are an attractive choice, especially for targeting cancer cells that often-over-express lipoprotein receptors figure 5. These features, together with their inherent biocompatibility as lipoproteins,

Table 3. Various protein-based nanocarriers for targeting surface-receptor-mediated drug delivery systems.

Protein nanocarrier	Ligand attached	Targeting surface receptor	Drug	Cancer cell	References
Bovine serum albumin	Folic acid	Folate receptor	Myricetin	MCF-7 (breast cancer cells)	[18]
Glutenin	Glucose	Glucose-transporter	Camptothecin	MCF-7	[77]
PEGylated Zein	Folic acid	Folate receptor	Paclitaxel	KB cells (oral cancer)	[78]
Bovine serum albumin	Folic acid	Folate receptor	Curcumin		[79]
Silk Fibroin	Folic acid	Folate receptor	Ibrutinib	HeLa, BT-474, and SKBR3	[80]
Bovine serum albumin	Folic acid	Folate receptor	Baicalin	MCF-7	[81]
Keratin	Folic acid	Folate receptor	Rutin	MCF-7	[62]
Bovine serum albumin	Biotin	Biotin receptor	Paclitaxel	MCF-7	[82]
Bovine serum albumin	Transferrin	Transferrin receptor	Apocycnin	Neuroprotection	[83]

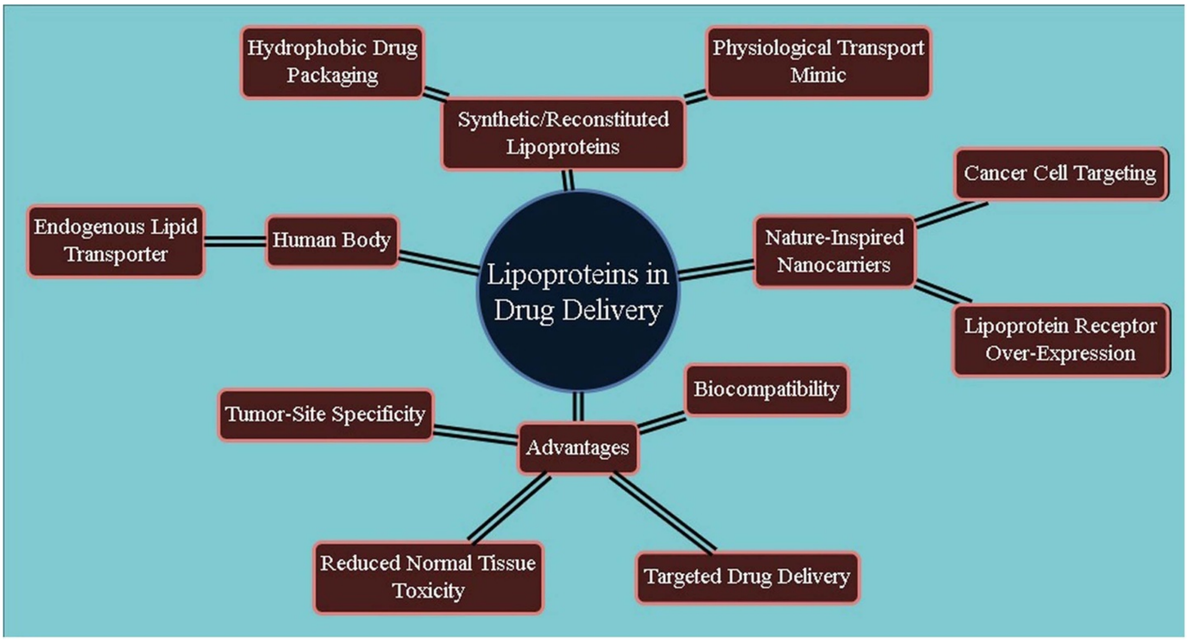

Figure 5. Diagram illustrates the role of lipoproteins in drug delivery, emphasizing tumor-site specificity, biocompatibility, targeted drug delivery, and reduced normal tissue toxicity through nature-inspired nanocarriers and synthetic lipoproteins.

define them to be an excellent choice for targeted drug delivery to cancer sites avoiding the normal tissue toxicity [76, 84]. Researchers have extensively explored albumin due to its high abundance in blood and excellent biocompatibility for drug delivery. Because albumin nanoparticles have excellent drug-loading capacity and the natural aggregation of cancer tissue, they are easily used as a powerful tool to enhance cancer therapy with hydrophobic drugs. One example is albumin-bound paclitaxel (Abraxane), which was approved by the FDA for use in breast and pancreatic cancers (figure 6). Functionalization of albumin nanoparticles using the ligands that bind to cancer cell surface marker receptors can further enhance drug accumulation in cancer sites [85].

Wheat and maize seeds contain gluten, a storage protein. Carbohydrates, starch, fat, and protein make up wheat gluten. Gliadin and glutenin make up gluten. It is separated into monomeric gliadin and polymeric glutenin according to its solubility. While polymeric glutenin is an alcohol-insoluble protein, monomeric gliadin is soluble in 70% ethanol. Because of disulphide bond cross-linking, glutenin has a molecular weight (MW) of 106 kDa and is insoluble in alcohol. Nanoparticles based on gliadin are extensively employed in the food, cosmetic, and pharmaceutical industries. Gliadin, however, is the cause of celiac disease, an autoimmune condition. Strong anionic/cationic charges seen in glutenin, another wheat protein derivative, have been shown to aid in the loading of a variety of drugs. It also has the ideal size, stability, and biocompatibility to be a drug carrier [32]. Zein, the corn's primary storage protein, has attracted scientific attention since its discovery in 1821. The four classes of zein are α-zein (two bands of average MW 22 and 24 kDa), β-zein (an average MW 17 kDa), γ-zein (two bands of average MW 18 and 27 kDa), and δ-zein (an average MW 10 kDa). Zein is actually a heterogeneous mixture of different peptides of various MWs. Nonpolar and uncharged amino acids, including glutamine (21%–26%), leucine (20%), proline (10%), and alanine (10%), make up the majority of zein's structural makeup [86]. Zein's low nutritional value and poor water solubility are caused by an imbalance in the amino acid makeup. However, zein has several advantageous qualities over other proteins due to its unique amino acid composition [87]. Zein is a hydrophobic protein that exhibits amphiphilic behavior, meaning it

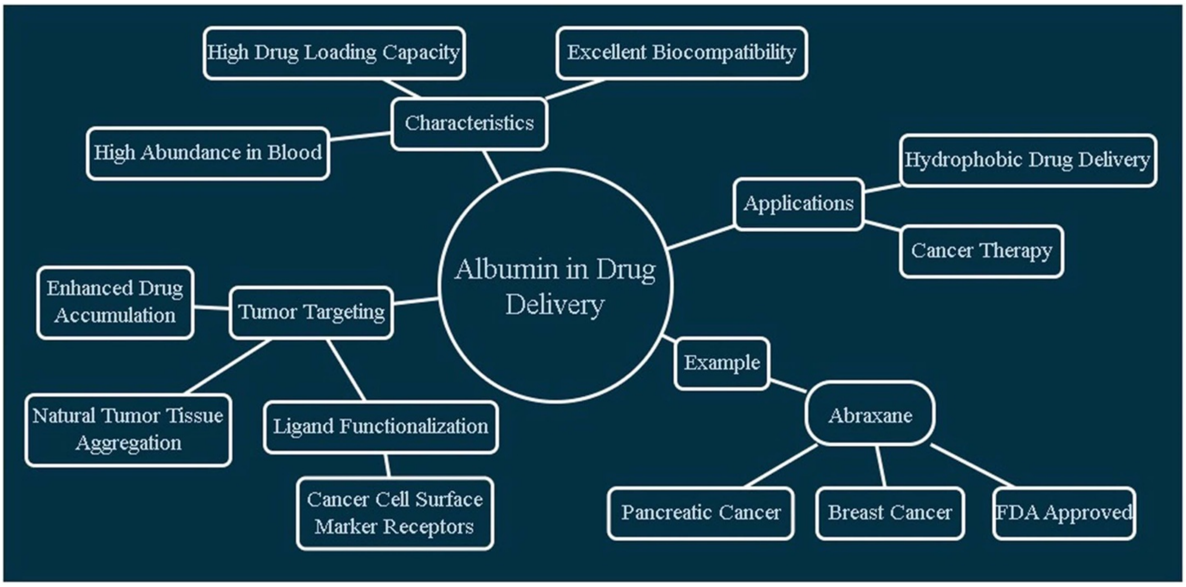

Figure 6. Diagram highlights albumin's role in drug delivery, showcasing its high drug loading capacity, biocompatibility, tumor targeting, and use in FDA-approved cancer therapies like Abraxane for breast and pancreatic cancer.

is insoluble in water except when alcohol (60%–95%), high urea concentrations, alkaline pH ($\geqslant$11), or anionic surfactants are present [88]. Zein can potentially physically entrap hydrophobic molecules and produce sustained medication release, which differs from drug delivery employing hydrophilic proteins. Additionally, zein is classified as generally regarded as safe and easily self-assembles into different-shaped nanoparticles based on the processing conditions and solvents used [89]. Zein has, therefore, been thoroughly researched for its ability to encapsulate and deliver bioactive ingredients [90]. Protein-polymer conjugates form hybrid structures in which the polymers give stability and tunability to proteins. The combination of both can help improve the pharmacokinetics *in vivo* because polymers can make way for protection against enzymatic degradation. The protein-polymer conjugates can be engineered to bind with certain receptors on the cancer cells, making it possible for selective drug delivery figure 7. Moreover, these conjugates can be designed to release the bioactive drug in response to particular stimuli, such as pH and enzymatic activation, thus significantly contributing to cancer treatment [91, 92].

7.2. Benefits of protein-based nanocarriers

Protein-based nanocarriers offer several advantages over conventional DDSs, particularly in the context of cancer therapy [46].

7.2.1. Improved drug-loading efficiency. Protein-based nanocarriers have key benefits among several DDSs, especially in cancer therapy. The structural malleability innate in proteins enables the capacity to encapsulate or polymerize a broad spectrum of therapeutic agents, including small molecules, peptides and nucleic acids. It will elevate the drug loading efficiency and enhance a greater concentration of anticancer agents to be delivered on cancer sites which leads to enhancement in therapeutic capabilities with a reduction in dose [93, 94].

7.2.2. Reduced toxicity and immunogenicity. Biocompatibility and biodegradability being proteins, one of the main advantages is their intrinsic properties being biomolecules. Protein-based nanocarriers, such as ferritin nanoparticles, are considered natural products by the immune system. Hence, they elicit lower immunogenicity and toxicity probability than their synthetic material counterparts. Most cancers cannot be squeezed into a simple blood-pressure cuff, and limiting the systemic toxicity of treatment is key to survival [95, 96].

7.2.3. Targeted delivery and prolonged circulation. Functionalizing protein-based nanocarriers with ligands that bind selectively to cancer cell surface receptors provides more specific drug delivery. It minimizes the off-target effects and increases therapeutic agent accumulation in cancer tissues. Protein-based carriers can also encapsulate the drugs and thus increase their circulation half-life in the bloodstream (due to protection from early degradation) as well as help achieve desired drug release kinetics leading to enhanced therapeutic efficacy [97, 98].

Protein-based nanocarriers serve as promising and efficient platforms in cancer therapy for better cancer drug delivery, site-specific treatment, and minimizing systemic toxicity. They can be engineered to take advantage of surface receptor

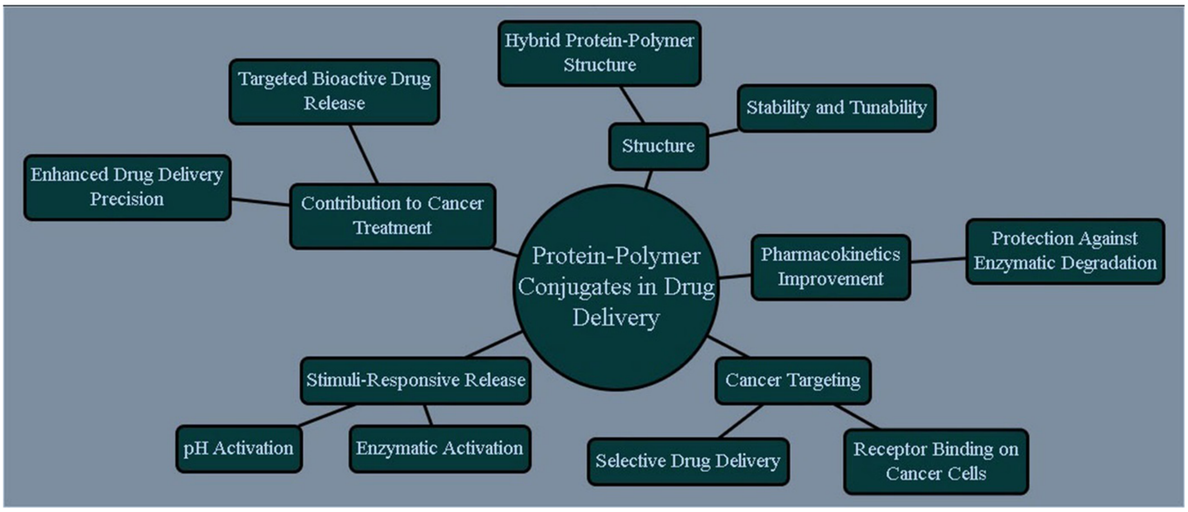

Figure 7. Diagram illustrates the role of protein-polymer conjugates in drug delivery, emphasizing their hybrid structure, stability, selective and stimuli-responsive release, enhanced pharmacokinetics, and targeted cancer therapy applications.

targeting, which allows them a path toward increased cancer treatment precision and, in turn, efficacy [97].

8. Applications in oncology

The use of protein-based nanocarriers is promising in the treatment of cancers for targeted delivery, providing an increase in therapeutic performance and reduced side effects on normal tissues. Protein-based nanocarriers possess superior targeting capabilities to many conventional chemotherapies since these delivery carriers are designed based on specific attributes of the particular tumor microenvironment and overexpressed surface receptors on cancer cells. Applications in Oncology-major applications of these carriers are tumor site targeted delivery, drug resistance mechanism and enhanced therapeutic efficacy for cancer [99, 100]. Protein-based nanocarriers are highly potent for treating various tumours due to therapeutic-specific delivery with less off-target toxicity in normal tissues. Once properly expressed on the surface of highly engineered delivery carriers, protein-based nanocarriers are superior in targeting compared to most traditional chemotherapies due to many attributes designed around that particular tumour microenvironment (TME) and common overexpressed cellular receptors found only on cancer cells figure 8. These carriers find their major applications for tumor site targeted delivery, drug resistance mechanism and superior therapeutic efficacy of the drugs against cancer [101, 102].

Passive drug loading of nanocarriers into tumor tissues is based on the EPR effect, which occurs due to impaired vascular function in tumors compared with normal tissue. The tumor microenvironment features leaky blood vessels that nanocarriers can pass through and enter. To improve the therapeutic efficacy of nanosized DDSs, we report that protein-based candles with biocompatible properties and tunable surfaces can take advantage of the EPR effect to deliver more drugs into tumour tissue. Additionally, they are usually less toxic and provide better safety than their synthetic analogs due to their natural origin [103, 104].

Using active targeting helps increase the specificity of drug delivery by adding ligands with receptors that are overexpressed specifically on cancer cells. Receptors such as folate, transferrin or EGFR are often overexpressed in tumors. These systems can be specifically conjugated ligands or antibodies on the surface of protein nanocarriers, binding to tumour cells and candidate cellular signaling pathways to facilitate receptor-mediated endocytosis. So the receptor-ligand interaction ensures that a maximum amount of drug is retained at the tumor site, thereby enhancing therapeutic efficacy and decreasing toxicity to non-target tissues [105].

9. Addressing drug resistance

Cancer drug resistance, especially MDR, currently poses a major challenge in the treatment of oncological diseases. Protein-based nanocarriers may circumvent this limitation [106, 107].

9.1. MDR in cancer

MDR is a main obstacle in chemotherapy of cancer and it was generally due to the overexpression of efflux pumps, such as P-gp, that can reduce intracellular drug concentrations. This, in turn, causes resistance to several chemotherapeutics in the survivors of these heterogeneous cell populations with local overexpression TNF-α, which maintains their collagenase ability within a hostile tumor microenvironment. Nanocarriers can be modified to circumvent MDR mechanisms and release their

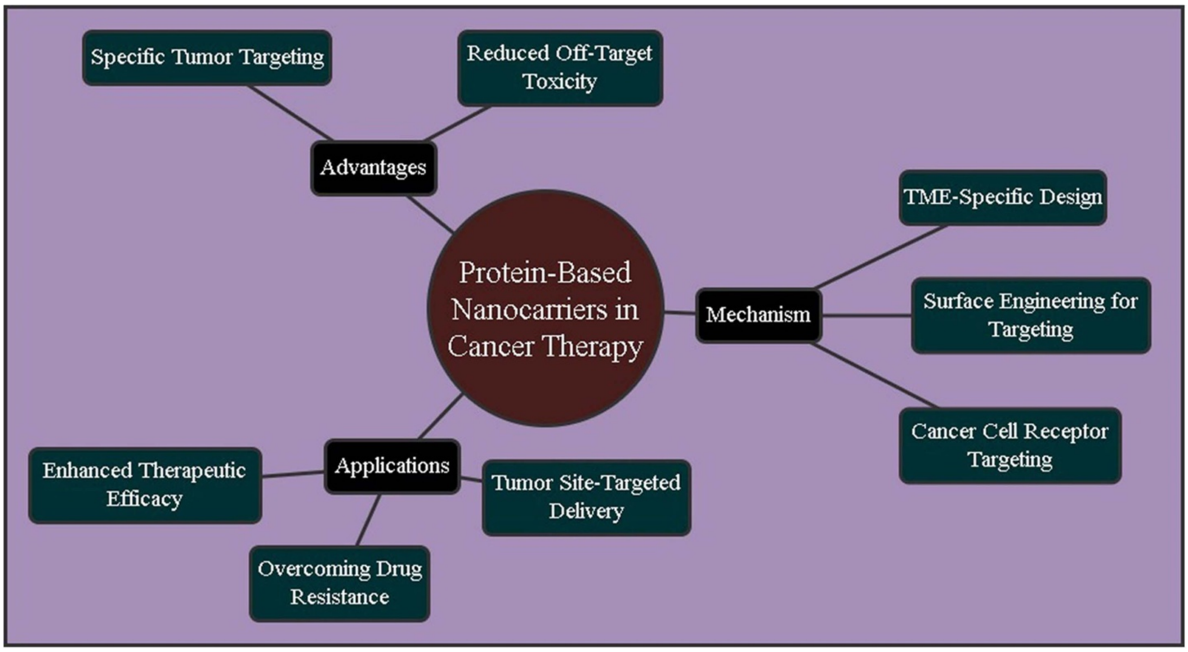

Figure 8. Diagram highlights the role of protein-based nanocarriers in cancer therapy, focusing on tumor-targeted delivery, advantages like reduced off-target toxicity, and mechanisms such as TME-specific design and receptor targeting.

therapeutic loads intracellularly upon entering cancer cells despite the presence of these efflux pumps [108].

9.2. Receptor-mediated uptake to bypass MDR

Protein-based nanocarriers developed towards transporter-mediated uptake are mainly used to liberate drugs, which will directly overcome MDR. Because the same receptors allowing drug resistance cytoplasmic drug internalization are also targeted for endocytosis, we may overcome this challenge by targeting those with these nanocarriers. This creates a stably-drug retaining condition even in resistant cancer cell populations and therefore ends up providing for one previously elusive cure to the issue of MDR solution [109, 110].

9.3. Improved therapeutic efficacy

This has positively enhanced the therapeutic effect of cancer on a wider scope; by using targeted delivery in combination with modalities to circumvent acquired drug resistance, overall efficacy can be significantly increased [111, 112].

9.3.1. Moderate pharmacokinetics. Protein-based nanocarriers frequently present superior pharmacokinetics and a slow-release profile, potentially keeping drugs active for prolonged periods. This sustained release significantly improves drug bioavailability and allows prolonged tumor retention resulting in superior therapeutic efficacy [113, 114].

9.3.2. Combination therapy approaches. Moreover, by creating protein-based nanocarriers, we may also potentiate cancer treatment when combined with other therapeutic agents or strategies, such as radiation and immunotherapy. These double agents, or interface approaches in combination therapy, reveal some synergy effect that hampers cells to develop second resistance and increases overall survival. By encapsulating different combinations of drugs or therapeutic agents in a targeted nanostructure, intelligent delivery systems can be designed which may have both additive and synergistic effects on cancer cells. Overall, using protein-based nanocarriers offers a potential opportunity for cancer treatment with targeted delivery systems resumed by overcoming drug resistance and enhancing therapeutic effectiveness. In oncology, this pathway gives cancer treatments a new breath of life and promises more targeted and less toxic therapies [115, 116].

10. Formulation approaches for receptor-targeted nanocarriers

Protein-based nanocarriers have emerged as a promising tool for delivering therapeutic agents in cancer therapy due to their biocompatibility, biodegradability, and ability to target specific receptors. One of the critical advancements in this area is the development of surface receptor-targeted protein-based nanocarriers. These nanocarriers are engineered to recognize and bind to specific receptors overexpressed on cancer cells, facilitating targeted delivery and reducing off-target effects. The following sections delve into the formulation approaches for these receptor-targeted nanocarriers, highlighting key techniques in protein engineering, drug loading, and characterization [117, 118].

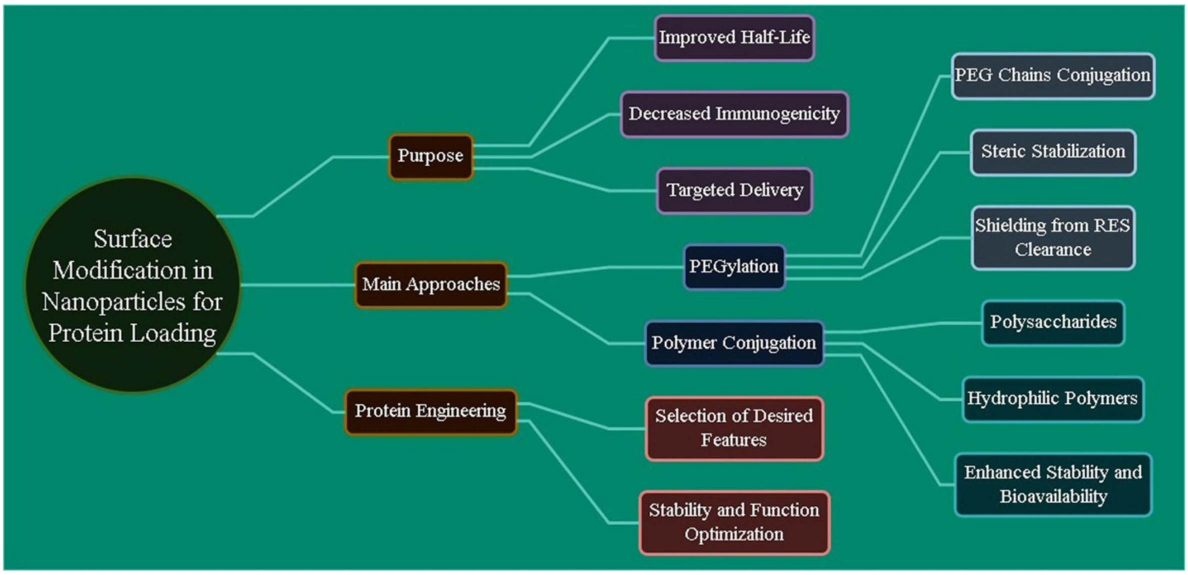

Figure 9. Diagram illustrates surface modification in nanoparticles for protein loading, focusing on purposes like improved half-life and targeted delivery, main approaches like PEGylation and polymer conjugation, and protein engineering for optimization.

10.1. Protein engineering for nanocarrier construction

Protein engineering is critical for building nanocarriers specifically for receptor-targeted drug delivery. Universal *in vivo* protein stabilization provides a flexible platform to enhance stability, biocompatibility and targeting specificity of nanocarriers for nearly any cancer cell receptor that can be targeted through ligand-coated nanoparticle-based therapy [119, 120].

10.1.1. Surface modification techniques. Surface modification is necessary for effective loading with proteins in nanoparticles and nanocarriers. These methods allow for protein engineering to select certain features like improved half-life, decreased immunogenicity and targeted delivery. The main approaches used PEGylation, conjugating polyethylene glycol (PEG) chains to the protein surface for steric stabilization and shielding from reticuloendothelial system clearance figure 9. Conjugation with other polymers like polysaccharides or hydrophilic polymers may also enhance the stability and bioavailability of nanocarriers [121, 122].

10.1.2. Ligand conjugation strategies. This is important because the modification of ligand attachment improves receptor-targeted nanocarriers for highly relevant drug delivery. Peptides, antibodies, or small molecules as ligands can be attached to the surface of nanocarriers for targeting specific cancer cell-targeting receptors. Covalent ligand attachment strategies, such as those using click chemistry or thiol-maleimide reactions, are often used to achieve stable and efficient binding of targeting ligands onto the surface nanocarrier [123, 124].

10.2. Drug-loading techniques

The targeting efficiency of a given nanocarrier is determined by its capability to co-localize with target cells and how efficiently it can encapsulate and deliver drugs. Different strategies are utilized to load drug molecules into the nanocarriers and simultaneously retain their biological activities [125, 126].

10.2.1. Drug loaded to NPs: covalent and non-covalent approaches. The drugs can be loaded covalently or non-covalently on the protein-based nanocarriers. It is a type of covalent drug loading. Here, the pharmacologically active compound and nanocarrier molecule are communicated through stable bonds, leading to controlled release over time. In contrast, non-covalent approaches employ second-order interactions, electrostatic interactions or hydrogen bonding to trap the drug inside its nanocarrier. Non-covalent loading is typically more suitable where drug release needs to be rapidly accomplished, or the modification of a therapeutic molecule with additional chemical groups should be avoided [127, 128].

10.3. Characterization of nanocarriers

Protein-based nanocarriers are essential for evaluating their activity, safety, and stability *in vitro* and *in vivo*. Different physicochemical properties of nanocarriers, such as size, surface charge and drug encapsulation efficiency, are crucial for their function in the delivery of drugs [129, 130].

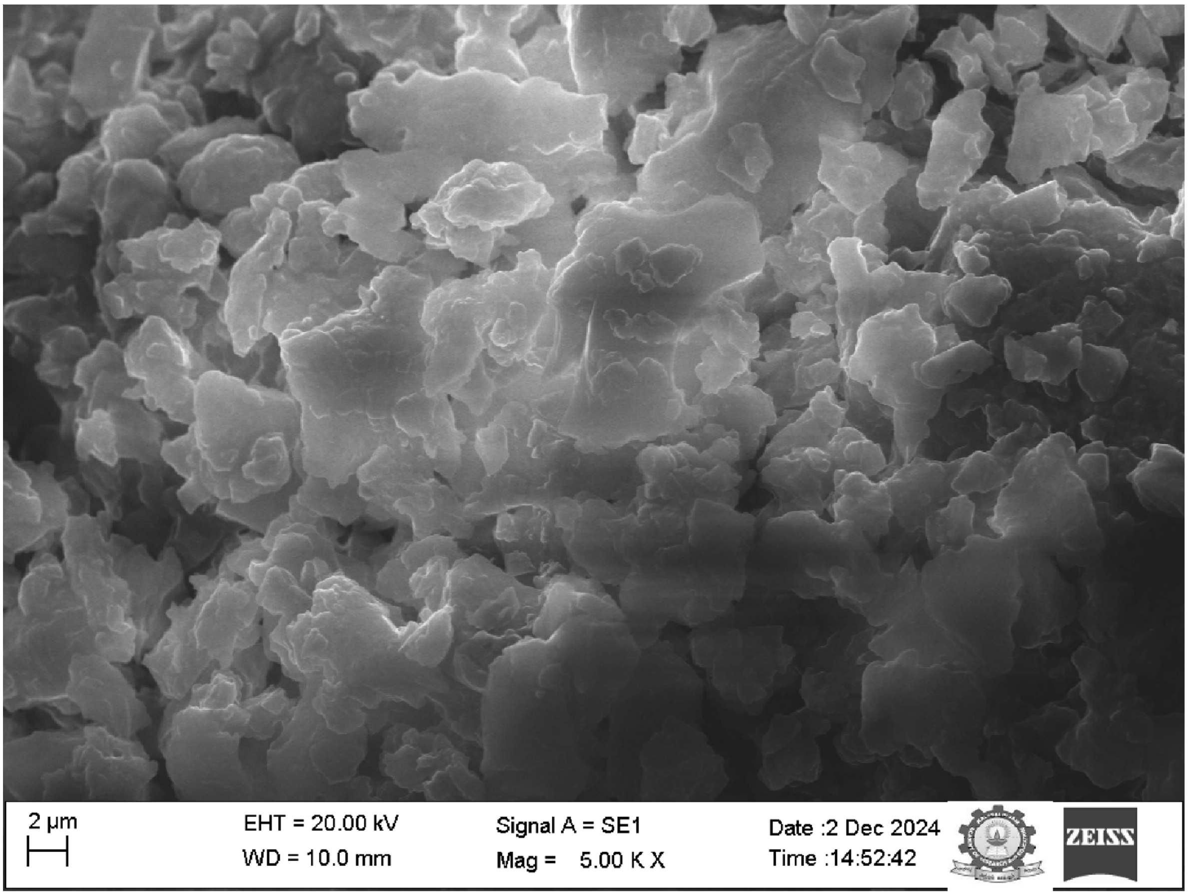

Figure 10. Schematic representation of SEM Image of protein-based nanocarriers highlighting their key attributes. The diagram illustrates tissue specificity achieved via surface modifications, ligand attachment, and targeted delivery. Functionalization involves multiple functional groups and modifiable binding capabilities.

10.3.1. Physicochemical properties. Physical characterization includes size, shape, and surface charge (zeta potential). The average hydrodynamic diameter of the nanocarrier is typically measured using the dynamic light scattering (DLS) approach. These parameters are usually calculated using DLS, transmission electron microscopy figure 10 and Fourier-transform infrared spectroscopy. These properties determine the bio-distribution, cellular uptake and release kinetics of the drug-loaded nanocarrier [131, 132].

10.3.2. In vitro *and* in vivo *evaluation.* Nanocarriers' *in vitro* and *in vivo* effectiveness need to be carefully assessed. *In vitro* cytotoxicity, cellular uptake, and drug release profiles of the nanocarrier are important to ensure before evaluations *in-vivo* for initial efficacy. They are mainly tested *in vivo*, which involves animal model systems to investigate the pharmacokinetics and biodistribution of the NP as well as its therapeutic efficacy. Overall, surface receptor-targeting protein nanocarriers represent a promising approach in the development of effective and targeted delivery strategies for anti-cancer drugs with reduced systemic toxicity [133, 134].

11. Future perspectives and challenges

In this regard, the evolution of protein-derived nanoscale particles for cancer therapy to pharmacologically target surface receptors has significantly increased therapeutic efficacy while minimizing off-target effects. Nevertheless, their clinical translation is challenging because several important roadblocks must be removed before these innovative strategies can be used regularly in cancer treatment. The development of protein-based nanocarriers has made substantial progress, but there are still limitations in clinical applications concerning immunogenicity, toxicity and manufacturing scale-up [135, 136].

Particularly in the clinic, immunogenicity of protein-based nanocarriers is among the main issues. However, most protein-based carriers are typically sourced from nature, which can result in immunogenic responses and, therefore, a quick half-life due to natural clearance. However, they are among the most immunogenic reactions and can form serious allergic responses. There are serious issues with modifying the protein structure to minimize immunogenicity. Still, functionality should also be maintained, which is a tedious and difficult part aside from affecting carrier drug delivery capability. The other major concern is toxicity. Some protein-based carriers are biocompatible, but they can still be cytotoxic in the presence of biological systems. Next, they look at the negative aspects of protein nanocarriers, for example accumulation in off-target tissues, causing toxic side effects. This is further complicated by the potential release of therapeutic agents in off-target sites, which can result in systemic toxicity and make their use clinically safer. The primary hurdle for these types of carriers has been the safety engineering to ensure that they conduct themselves only in cancerous cells and with minimal off-target effects [137, 138].

The challenge of scaling up for the clinical translation protein-based nanocarriers is also very important. Other problems with any translated carrier would appear at this stage as patient class production must be quality and consistency ensured. However, manufacturing of these carriers at a scale necessary for clinical use involves intricate control over protein engineering, formulation strategies and quality assurance protocols. It is also important to guarantee that the nanocarrier features, including size, shape and surface properties, are reproduced in order to have similar therapeutic effects. Addressing these challenges involves the progression of biomanufacturing technology, including scalable and economic approaches to fabricate nanocarriers [139, 140].

12. Future directions

12.1. Next-generation protein-based nanocarriers

Finally, future protein-based nanocarriers will likely overcome many of the challenges faced today by utilizing and optimizing advanced materials that can be accessed only by employing cutting-edge engineering techniques. These carriers will be preferentially designed to enhance delivery, minimize immunogenicity and maximize targeting. Integration of synthetic peptides or recombinant proteins via protein engineering has been proposed to improve these nanocarriers' biocompatibility and functional versatility. Additionally, responsive components and precise drug-releasing pH-sensitive or enzyme-specific targeting mechanisms have to be involved in constructing the specific release profile to overcome off-target side effects while promoting therapy outcomes [141, 142].

12.2. Advancements in targeting strategies

In the future, targeted protein systems will rely on further development of targeting paradigms with improved abilities to selectively and efficaciously deliver proteins. Improvements in ligand conjugation approaches will enable the grafting of several targeting moieties, resulting in dual or multi-targeted delivery platforms. These systems can be multi-targeting, meaning they act on various receptors or pathways related to cancer progression and improve selectivity for the carrier between healthy and tumoral cells. Besides, advanced methods by aptamers, small molecules and antibodies for surface receptor targeting will enhance the accuracy of these nanocarriers [143, 144].

12.3. Personalized cancer therapies

The merging of personalized medicine with protein-based nanocarrier systems is an exciting aspect to steer toward. It provides patient-specific targeted nanocarrier delivery by employing the molecular profile of each individual cancer. This not only increases the therapeutic efficacy level but also curtails side effects. The emergence of genomic data and breakthroughs in bioinformatics are bringing the ability to design personalized protein-based nanocarriers for cancer therapy within reach. These customized treatments done in the future could fundamentally change cancer care by providing hugely effective and tailored treatment options for every patient [145, 146].

13. Conclusion

The surface receptor-targeted protein-based nanocarriers review mentions that these carriers provide enormous research interests in cancer therapy. This will provide site-specific delivery for therapeutic agents, which minimizes the non-target toxicity usually linked with conventional treatments such as chemotherapy. Engineered protein nanocarriers can be designed to bind with high specificity through targeted receptors overexpressed in cancer cells, keeping drug delivery on target and improving both therapeutic efficacy and prevention of damage at healthy tissues. This will help enhance the safety margins of cancer treatment regimens and, at the same time meet many unmet clinical challenges such as drug resistance or lack of bioavailability to chemotherapy agents. Protein-based nanocarriers have inherent biocompatibility and naturally degrade within the biological system, which gives protein an edge over synthetic polymers. The carriers can be crafted to break down harmlessly in the body, thus preventing problems such as long-term toxicity or immune response. Moreover, the versatility of protein engineering makes possible multifunctional nanocarriers that are adept at transporting drugs and imaging agents, promoting applications in cancer therapy. Still, there are obstacles on the path to clinical translation of this approach. Despite their great potential in clinical applications, Protein-based nanocarriers still exhibit the problems associated with immunogenicity, less feasibility of large-scale production and on-time quality control. These issues need to be realized in future nanocarrier research at its best, echeloning colossally for the personalization of cancer-crushing. Based on all these, protein-based nanocarriers offer great potential for molecular-targeted cancer therapy. They can seek out cancer cells because they attach to another protein on the surface of a cell, so this targeting approach gives potential vast promise in both making drugs work better and reducing side effects. With further breakthroughs in protein engineering, drug loading and ligand binding strategies, these nanocarriers may provide a platform along which to tailor-make bespoke cancer remedies with unparalleled therapeutic index for future patients.

Data availability statement

No new data were created or analysed in this study.

Acknowledgment

We would like to extend our heartfelt gratitude to the management and administration of Vels Institute of Science, Technology & Advanced Studies, Pallavaram, Chennai 600117, India and Kalasalingam Academy of Research and Education, Krishnankoil, Tamil Nadu, for providing all support.

Author contributions

P T and S K contributed to the study's conception, design, and data validation. PT and SK wrote the original manuscript. P T, P P, S V, P P and S K proofread it. All the authors have read and approved the manuscript for submission.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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